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Empiric quinidine therapy for asymptomatic Brugada syndrome: Time for a prospective registry

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Keywords

Brugada syndrome; Quinidine; Electrophysiologic study; Ventricular fibrillation

Our present therapeutic approach to asymptomatic Brugada syndrome is probably causing more harm than good.¹ All over the world, patients with asymptomatic Brugada syndrome are undergoing electrophysiologic studies (EPS)^{2,3}; depending on the aggressiveness of the EPS protocol, 20% to 80% of such patients will have inducible ventricular fibrillation (VF),^{2–6} and many will undergo implantation of an implantable cardioverter defibrillator (ICD).^{2–6} However, the rate of spontaneous VF among patients undergoing prophylactic ICD implantation for “asymptomatic Brugada syndrome with inducible VF” seems to be only 1% per year according to a multicenter European study.⁷ Accordingly, ICD implantation might be unnecessary for the vast majority of patients. On the other hand, 28%⁷ to 32%⁶ of these young individuals develop very serious complications directly related to ICD implantation. Thus, the wisdom of guiding our therapeutic approach by the results of EPS has been questioned.⁸

Perhaps it is time to apply our experience with the long QT syndrome (LQTS) to the Brugada syndrome. As in Brugada syndrome, cardiac arrest may be the presenting symptom in LQTS. Based on nonrandomized studies showing that beta-blockers dramatically reduce the arrhythmic risk, empiric drug therapy with beta-blockers has been the first line of therapy for the LQTS for more than 30 years.⁹ All asymptomatic LQTS patients nowadays receive beta-blocker therapy, and prophylactic ICD implantation is reserved for some of the patients with high-risk characteristics such as “genotype other than LQT1 and QTc >500 msec.”¹⁰ Of note, collecting data about the value and limitations of empiric beta-blocker therapy^{10–14} was possible only because the LQTS was described—and had to be treated—before the ICD became widely available.¹⁵ Numerous patients with LQTS have safely received empiric beta-blocker therapy for many years; yet, it is reasonable to assume that many of them would have undergone unnecessary ICD implantation had the LQTS been first described in the ICD era. With all the abovementioned concepts in mind, we will attempt to explain why empiric drug therapy with quinidine may be better than EPS-guided ICD implantation for the primary prevention of arrhythmic death in asymptomatic patients with Brugada syndrome.

Why is it that the EPS-guided approach is not working?

There is general agreement that the risk for cardiac arrest for patients with negative EPS is only 1% to 2%.¹⁻³ It should be emphasized, however, that these low values relate to a mean follow-up period of less than 4 years.³ The long-term risk for patients with asymptomatic Brugada syndrome and negative EPS could conceivably be higher. Obviously, the negative predictive value of EPS will depend on the aggressiveness of the EPS protocol used. Unfortunately, using more aggressive EPS protocols to improve the negative predictive value, particularly if including extrastimulation with very short coupling intervals, would inevitably reduce the positive predictive value of the test as well.¹⁶

Understanding the significance of a positive EPS in the asymptomatic patient is even more problematic.¹ To begin with, one should realize that it is possible to induce VF with double or triple ventricular extrastimulation in at least 6% of healthy individuals.¹ In fact, the rate of accidental VF induction could be much higher than 6% because (as explained in detail elsewhere¹) 6% to 41% of the healthy individuals participating in the 5 studies¹⁷⁻²¹ looking at the specificity of inducible VF did not go through the entire EPS protocol because the study was terminated prematurely to avoid the need for DC shock when nonsustained polymorphic ventricular tachycardia was induced.

Defining the positive predictive value of EPS in patients with asymptomatic Brugada syndrome is even more problematic.^{8,22} On the one hand, Brugada et al^{4,5} have presented data showing that 12% of asymptomatic patients with inducible VF will have cardiac arrest (or spontaneous ventricular arrhythmias triggering ICD therapy) within 3 years of follow-up. On the other hand, data from 10 published studies (summarized by Paul et al³) including data for more than 250 patients with inducible VF suggest that the risk is no more than 4%.¹ As explained elsewhere,³ the higher (12% risk) figures published by Brugada et al probably resulted from overrepresentation of patients with more severe forms of the disease in their earlier series.

Why are the complication rates after ICD implantation for Brugada syndrome so high?

It is not surprising that the complication rate after ICD implantation for Brugada syndrome (28% in a multicenter European study)⁷ is higher than the 12% complication rate reported in the Antiarrhythmic Versus Implantable Defibrillators (AVID) trial.²³ AVID patients had organic heart disease, and consequently 16% of them died within 18 months of ICD implantation.²⁴ The much longer survival of patients with Brugada syndrome (who are young and free of heart disease) inevitably places them at increased risk for ICD-related complications in the long term because the repeated need for ICD replacements significantly increases the risk of device-related infection.²⁵ Also, the risk for electrode fractures increases over time, especially in young active male patients.²⁶ Patients with Brugada syndrome are also at increased risk for ICD-related complications in the short term because they are physically active, tend to have atrial arrhythmias,²⁷⁻²⁹ and do not receive beta-blockers. T-wave oversensing in patients with Brugada syndrome with implanted ICD is also a well-described complication.³⁰ All of these factors significantly increase their risk for inappropriate shocks,^{6,7,26,30} which seriously impair quality of life. In 2 recent European studies, 20%⁷ to 36%²⁶ received inappropriate ICD shocks because of sinus tachycardia, atrial arrhythmias, T-wave oversensing, or lead malfunction. Young age, history of atrial arrhythmias, or T-wave over-sensing at the time of ICD implantation were predictors of inappropriate shocks.

Many patients and physicians are finding the abovementioned morbidity intolerable, particularly after prophylactic ICD implantation. The search for alternative therapeutic strategies, such as empiric prophylactic therapy with quinidine, is therefore justifiable.

Why quinidine?

The Brugada syndrome has been associated with mutations affecting sodium, calcium, and potassium channels subunits.³¹⁻³⁶ Irrespective of the ion channel involved, a prominent ITo (transient outward potassium current) seems to play a predominant role in arrhythmogenesis.³⁷ Consequently, blocking the ITo channel is a logical approach and this can be done with quinidine.³⁷ Indeed, the following lines of evidence support the use of quinidine for the primary prevention of arrhythmic death in Brugada syndrome: (1) Quinidine prevents phase II reentry and VF in the wedge preparation that mimics Brugada syndrome in vitro.³⁷ (2) Quinidine may normalize the electrocardiogram in a few patients.³⁸ (3) Quinidine is extremely effective in preventing the induction of VF in humans during EPS (76%³⁹ to 88%⁴⁰ of patients who have inducible VF at baseline EPS are rendered noninducible by quinidine therapy). (4) Quinidine is very effective for terminating VF storms when other drugs fail.^{41,42} (5) Nonrandomized studies suggest that quinidine prevents spontaneous arrhythmias in high-risk patients with Brugada syndrome during long-term follow-up.^{39,40} In fact, Belhassen et al⁴⁰ have effectively used quinidine as the sole therapy (without ICD back-up) for patients with symptomatic Brugada syndrome, including patients who had spontaneous VF before the initiation of therapy. In a recent study, none of the 50 patients with symptomatic or asymptomatic Brugada syndrome developed symptomatic ventricular arrhythmias while on quinidine therapy during a follow-up period ranging from 3 months to more than 10 years.⁶

Risk versus benefit considerations of empiric quinidine in Brugada syndrome

Quinidine often causes side effects (such as diarrhea, thrombocytopenia, hepatitis) that resolve after drug discontinuation. When high doses of quinidine are used,⁴⁰ 1 of 3 patients receiving empiric quinidine have to discontinue the medication because of drug intolerance. On the other hand, excellent long-term tolerability has been reported for patients with Brugada syndrome receiving low doses of quinidine.⁴³

The main concern relates to the potential proarrhythmic risks of quinidine. A 2% to 8% risk for torsades de pointes from quinidine has been estimated, and this risk does not seem to increase with higher doses.⁴⁴ However, these figures mainly reflect the risk for patients with organic heart disease.⁴⁴ Also, male gender decreases the risk of drug-induced torsades de pointes,⁴⁵ and the vast majority of patients with Brugada syndrome are males. Finally, most cases of quinidine-induced torsades de pointes occur soon after the onset of therapy,⁴⁶ and close monitoring during the first 3 days of therapy should prevent proarrhythmic complications. Torsades de pointes occurring long after the onset of therapy is often caused by drug interactions or hypokalemia,⁴⁷ and meticulous avoidance of such risk factors should reduce the risk of torsades de pointes from quinidine in patients with Brugada syndrome to a minimum.

A prospective registry of empiric quinidine for asymptomatic Brugada syndrome

A Prospective Registry will recruit patients with asymptomatic Brugada syndrome. The study appears at the National Institutes of Health website (ClinicalTrials.gov) and can be accessed at <http://clinicaltrials.gov/ct2/show/NCT00789165?term=brugada&rank=2>.

Brugada syndrome will be defined according to the Second Consensus Conference,⁴⁸ and patients will be considered asymptomatic if they do not have a history of cardiac arrest or a history of arrhythmic syncope with malignant clinical characteristics suggesting arrhythmic origin. In other words, patients reporting palpitations, atypical chest pain, and/or a history of syncope with clinical characteristics strongly suggestive of benign vasovagal syncope will be counted as asymptomatic and will be accepted into the trial (Figure 1). The study encourages empiric therapy with hydro-quinidine hydrochloride (Serecor, Sanofi-Aventis, France, 600 to 900 mg/day; <http://drugs-about.com/drugs/serecor.html>). Lower doses of quinidine have been associated with a higher incidence of inducibility of VF during repeated EPS.⁴³ However, the effects of low-dose quinidine for preventing spontaneous arrhythmias is less clear, and reduced doses are clearly associated with better long-term tolerability.⁴³ Therefore, patients developing adverse events have the option of continuing low doses of quinidine (such as 300 mg at bedtime). Also, such patients may then opt to undergo EPS (with subsequent ICD implantation if the EPS is positive) or may prefer follow-up with no therapy. Finally, in view of recent data suggesting that unselected patients with asymptomatic Brugada syndrome are at low risk for developing spontaneous VF, it is recognized that physicians and patients may prefer to avoid antiarrhythmic therapy altogether. Such patients are also welcome to join the Registry (Figure 1).

References

1. Viskin S, Rogowski O. Asymptomatic Brugada syndrome: a cardiac ticking time-bomb? *Europace*. 2007; 9:707–710. [PubMed: 17715171]
2. Gehi AK, Duong TD, Metz LD, et al. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. *J Cardiovasc Electrophysiol*. 2006; 17:577–583. [PubMed: 16836701]
3. Paul M, Gerss J, Schulze-Bahr E, et al. Role of programmed ventricular stimulation in patients with Brugada syndrome: a meta-analysis of worldwide published data. *Eur Heart J*. 2007; 28:2126–2133. [PubMed: 17483540]
4. Brugada P, Brugada R, Mont L, et al. Natural history of Brugada syndrome: the prognostic value of programmed electrical stimulation of the heart. *J Cardiovasc Electrophysiol*. 2003; 14:455–457. [PubMed: 12776858]
5. Brugada P, Geelen P, Brugada R, et al. Prognostic value of electrophysiologic investigations in Brugada syndrome. *J Cardiovasc Electrophysiol*. 2001; 12:1004–1007. [PubMed: 11573688]
6. Rosso R, Glick A, Glikson M, et al. Outcome after implantation of ICD in patients with Brugada syndrome: a multicenter Israeli study (ISRABRU). *Isr Med Assoc J*. 2008; 10:435–439. [PubMed: 18669142]
7. Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverterdefibrillator in patients with Brugada syndrome: a multicenter study. *Circulation*. 2006; 114:2317–2324. [PubMed: 17116772]
8. Priori SG, Napolitano C. Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing? *Circulation*. 2005; 112:279–292. discussion 279–292. [PubMed: 16013094]
9. Schwartz PJ, Periti M, Malliani A. The long Q-T syndrome. *Am Heart J*. 1975; 89:378–390. [PubMed: 234667]
10. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA*. 2004; 292:1341–1344. [PubMed: 15367556]
11. Chatrath R, Bell CM, Ackerman MJ. Beta-blocker therapy failures in symptomatic probands with genotyped long-QT syndrome. *Pediatr Cardiol*. 2004; 25:459–465. [PubMed: 15534720]
12. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation*. 2000; 101:616–623. [PubMed: 10673253]

13. Moss AJ, Shimizu W, Wilde AA, et al. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation*. 2007; 115:2481–2489. [PubMed: 17470695]
14. Villain E, Denjoy I, Lupoglazoff JM, et al. Low incidence of cardiac events with beta-blocking therapy in children with long QT syndrome. *Eur Heart J*. 2004; 25:1405–1411. [PubMed: 15321698]
15. Schwartz PJ. The idiopathic long QT syndrome: the need for a prospective registry. *Eur Heart J*. 1983; 4:529–531. [PubMed: 6641746]
16. Eckardt L, Probst V, Smits JP, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. *Circulation*. 2005; 111:257–263. [PubMed: 15642768]
17. Belhassen B, Shapira I, Sheps D, et al. Programmed ventricular stimulation using up to two extrastimuli and repetition of double extrastimulation for induction of ventricular tachycardia: a new highly sensitive and specific protocol. *Am J Cardiol*. 1990; 65:615–622. [PubMed: 2309631]
18. Brugada P, Green M, Abdollah H, et al. Significance of ventricular arrhythmias initiated by programmed ventricular stimulation: the importance of the type of ventricular arrhythmia induced and the number of premature stimuli required. *Circulation*. 1984; 69:87–92. [PubMed: 6689650]
19. Buxton AE, Waxman HL, Marchlinski FE, et al. Role of triple extrastimuli during electrophysiologic study of patients with documented sustained ventricular tachyarrhythmias. *Circulation*. 1984; 69:532–540. [PubMed: 6692515]
20. Morady F, Shapiro W, Shen E, et al. Programmed ventricular stimulation in patients without spontaneous ventricular tachycardia. *Am Heart J*. 1984; 107:875–882. [PubMed: 6720516]
21. Stevenson WG, Brugada P, Waldecker B, et al. Can potentially significant polymorphic ventricular arrhythmias initiated by programmed stimulation be distinguished from those that are nonspecific? *Am Heart J*. 1986; 111:1073–1080. [PubMed: 3716980]
22. Brugada P, Brugada R, Brugada J. Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing? *Circulation*. 2005; 112:279–292. discussion 279–292. [PubMed: 16009809]
23. Kron J, Herre J, Renfro EG, et al. Lead- and device-related complications in the antiarrhythmics versus implantable defibrillators trial. *Am Heart J*. 2001; 141:92–98. [PubMed: 11136492]
24. The Antiarrhythmic Versus Implantable Defibrillators (AVID) investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997; 337:1576–1583. [PubMed: 9411221]
25. Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation*. 2007; 116:1349–1355. [PubMed: 17724263]
26. Sarkozy A, Boussy T, Kourgiannides G, et al. Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome. *Eur Heart J*. 2007; 28:334–344. [PubMed: 17251258]
27. Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. *Europace*. 2007; 9:947–950. [PubMed: 17540664]
28. Kusano KF, Taniyama M, Nakamura K, et al. Atrial fibrillation in patients with Brugada syndrome relationships of gene mutation, electrophysiology, and clinical backgrounds. *J Am Coll Cardiol*. 2008; 51:1169–1175. [PubMed: 18355654]
29. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol*. 2002; 40:1437–1444. [PubMed: 12392834]
30. Stix G, Bella PD, Carbucicchio C, et al. Spatial and temporal heterogeneity of depolarization and repolarization may complicate implantable cardioverter defibrillator therapy in Brugada syndrome. *J Cardiovasc Electrophysiol*. 2000; 11:516–521. [PubMed: 10826930]
31. Antzelevitch C, Pollevick GD, Cordeiro JM, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation*. 2007; 115:442–449. [PubMed: 17224476]
32. Chen Q, Kirsch G, Zhang D, et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature*. 1998; 392:293. [PubMed: 9521325]

33. London B, Michalec M, Mehdi H, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na⁺ current and causes inherited arrhythmias. *Circulation*. 2007; 116:2260–2268. [PubMed: 17967977]
34. Schulze-Bahr E, Eckardt L, Breithardt G, et al. Sodium channel gene (SCN5A) mutations in 44 index patients with Brugada syndrome: different incidences in familial and sporadic disease. *Hum Mutat*. 2003; 21:651–652. [PubMed: 14961552]
35. Delpón E, Cordeiro JM, Núñez L, et al. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ Arrhythmia Electrophysiol* doi. 2008; 1:209–218.
36. Watanabe H, Koopmann TT, Le Scouarnec S, et al. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J Clin Invest*. 2008; 118:2260–2268. [PubMed: 18464934]
37. Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. *J Cardiovasc Electrophysiol*. 2001; 12:268–272. [PubMed: 11232628]
38. Alings M, Dekker L, Sadee A, et al. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. *Pacing Clin Electrophysiol*. 2001; 24:1420–1422. [PubMed: 11584468]
39. Hermida JS, Denjoy I, Clerc J, et al. Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol*. 2004; 43:1853–1860. [PubMed: 15145111]
40. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation*. 2004; 110:1731–1737. [PubMed: 15381640]
41. Ohgo T, Okamura H, Noda T, et al. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. *Heart Rhythm*. 2007; 4:695–700. [PubMed: 17556186]
42. Marquez MF, Salica G, Hermosillo AG, et al. Ionic basis of pharmacological therapy in Brugada syndrome. *J Cardiovasc Electrophysiol*. 2007; 18:234–240. [PubMed: 17338775]
43. Mizusawa Y, Sakurada H, Nishizaki M, et al. Effects of low-dose quinidine on ventricular tachyarrhythmias in patients with Brugada syndrome: low-dose quinidine therapy as an adjunctive treatment. *J Cardiovasc Pharmacol*. 2006; 47:359–364. [PubMed: 16633076]
44. Jackman WM, Friday KJ, Anderson JL, et al. The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis*. 1988; 31:115–172. [PubMed: 3047813]
45. Viskin S. The long QT syndromes and torsade de pointes. *Lancet*. 1999; 354:1625–1633. [PubMed: 10560690]
46. Viskin S, Barron HV, Heller K, et al. The treatment of atrial fibrillation: pharmacologic and nonpharmacologic strategies. *Curr Prob Cardiol*. 1997; 22:44–108.
47. Viskin, S.; Fish, R.; Roden, DM. Braunwald, E.; Fauci, SA.; Isselbacher, KJ., et al., editors. Drug induced torsade de pointes. *Harrison's Principles of Internal Medicine*. Harrison's on-line. Available at: <http://harrisonsonline.com>. 14 ed; 2000:231
48. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference. *Heart Rhythm*. 2005; 2:429–440. [PubMed: 15898165]

Figure 1. Prospective registry of empiric quinidine for asymptomatic Brugada syndrome. For definition of asymptomatic Brugada syndrome, see text.